thereby inducing a semi-synchronous wave of liver cell proliferation *in vivo*, which treats or prevents cirrhosis of the liver.

Applicants respectfully submit the above Amendment including (1) a clean version of the rewritten amended claims in accord with 37 CFR §1.121(c)(1)(i) and (2) a marked-up version of the rewritten amended claims in accord with 37 CFR §1.121(c)(1)(ii). Applicants respectfully request entry of these amendments.

REMARKS

I. Oath/Declaration

The Office action states that the "oath or declaration is defective" on the ground that the declaration submitted does not refer to the preliminary amendments filed with the continuation application. Applicants respectfully request withdrawal of this rejection. MPEP §602.05(a) states, in part,

> "A copy of the oath or declaration from a prior non-provisional application may be filed in a continuation or divisional application even if the specification for the continuation or divisional application is different from that of the prior application, in that revisions have been made to clarify the text to incorporate amendments made in the prior application, or to make other changes provided the changes do not constitute new matter relative to the prior application."

The declaration filed with the instant application is a copy of the declaration from prior non-provisional application Serial No. 09/256,630. As a result, Applicants submit that the declaration filed with the instant application is not defective and the filing of a new oath or declaration is not required.

II. 35 U.S.C. §112, ¶1

Because there are a number of 112(1) rejections on pages 3-10 of the present office action, Applicants have divided the rejections and corresponding responses into five basic categories:

(1) Claims 28-51 do not encompass all diseases or conditions;
(2) Claims 28-51 are enabled for treating cirrhosis and satisfy the "how to use" requirement;
(3) The present invention is an effective method of treating cirrhosis;
(4) The gene therapy methods of the present invention are not unpredictably vague; and
(5) Rat systems are effective models of human systems.

Applicants have then categorized various rejections under the most appropriate category. Given the interrelated nature of enablement rejections, some areas might be discussed in more than one category, if relevant.

(1) Claims 28-51 do not encompass all diseases or conditions.

Claims 28-51 have been rejected under 35 U.S.C. §112, first paragraph, for the reason that the claims are "broad enough to encompass the treatment of any disease or condition of the human or animal body, including diseases outside of the liver." (Jan. 17, 2002 OA, p.3). Applicants have amended independent claims 28 and 35 from "a method of treatment comprising" to "a method of treating diseases associated with the liver comprising." This

amendment limits the claims to treating liver and liver-related diseases specifically involving liver cells and thus overcomes the objection by showing that the claims are not directed to any disease or condition unrelated to the liver. Claim 51 is directed specifically to "a method for treating or preventing cirrhosis of the liver" so there can be no confusion that this claim would be useful for "treating diseases of the brain" (01.17.02 OA, p.3).

(2) Claims 28-51 are enabled for treating cirrhosis and satisfy the "how to use" requirement.

The next 112(1) rejection, found throughout p. 4-10, is for lack of enablement requiring undue experimentation in order for one skilled in the art to use the invention. The office action states that the invention "does not disclose the method for treating or preventing cirrhosis of the liver. The specification does not disclose any protocols or steps, and thus, does not satisfy the 'how to use' requirement of 35 U.S.C. 112, to practice the invention of claims 28-51, whereby the claimed therapeutic effect would result." (Jan. 17, 2002 Office Action, p. 4). The office action goes on to say that "examples in the specification do not disclose a therapeutic effect in the individuals after therapy with the said composition and/or the efficacy of the composition in treating cirrhosis of the liver." Id. Applicants respectfully traverse.

Initially, Applicants respectfully submit that the office action has applied too stringent a standard as to what the specification must show in order to be considered an enabling disclosure for the claimed invention. In particular, the office action would apparently require the specification to show that the technique has actually produced a therapeutic effect in a person. However, this is not what the law requires. In re Brana, 34 USPQ2d 1436, 1442

(Fed. Cir. 1995) ("We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.")

Secondly, there are many locations in which the specification gives specific direction on how to make and use the present invention. In particular, for a given species, the practitioner may first follow the general procedures set forth at p. 21, lines 1-24 and Example 1, p. 23, lines 11-16 of the specification, to establish a dose response curve for KGF and T3 independently on in vivo liver cell proliferation for that species. The practitioner may then establish a time course independently for each of the individual factors, as taught in the specification in Example 2, p. 23, line 16 through p. 24, line 7. It is significant that the office action acknowledges that the skill of an artisan in this subject area is "very high." (Jan. 17, 2002 OA, pp. 4 and 7). Applicants suggest that, after pointing out specific guidance in the specification for carrying out the present invention, the claims should be allowed because these highly skilled artisans are capable of moving forward with the guidance provided in the present specification.

After determining the optimal dose and timing for the administration of each of the factors independently, the practitioner administers the factors in such doses and at such times determined to give best results for that species. The practitioner may do this, for example, as disclosed in the specification at p. 24, line 8 through p. 25, line 8, Example 3, thus determining the effect of co-administering the factors, each at its optimal dose and timing.

Significantly, Examples 5 (p. 25, line 20 through p. 26, line 22) and 6 (p. 27, lines 1 though 14) also teach successful transfection and increased expression of a gene product using the present method.

The office action states on page 6 that the specification does not teach what mode of administration would result in expression at the appropriate site. But Applicants refer to p. 8, lines 10-17 of the specification that explicitly discusses possible modes of administration and indicates a preference for subcutaneous administration. The office action also states that "there is no specific guidance regarding the amount of vector to be administered, the frequency of administration and the level of expression required for the treatment to be therapeutically effective." (OA, p. 6). Applicants refer to p. 12, line 10 through p. 15, line 2 of the specification that discusses the above-listed concern, indicating that, while the specification recommends that the timing, dosage and mode be determined by the treating medical professional, it does indicate preferred ranges. ("Most preferably, the vector is administered between about 24 hours and about 8 days after factor administration." p. 12, lines 16-17). The specification also indicates that successive administrations are preferably done at between 6 and about 24 hours. (p. 12, lines 21-22).

Thus, the specification clearly gives direction regarding administration and dosage of the vector in relation to the stimulatory factors. The specification also gives the exact and specific timing and dosages used in all of the experimental models presented in the Examples. Those of skill in the art, having familiarity with translating treatment of rat subjects to treatment of human subjects should be able to discern the appropriate dosages given the individual needs of the patient.

In conclusion, Applicants submit that undue experimentation is not required of one of ordinary skill in the art following the procedures described in detail in the specification. Given the disclosure in Applicants' specification, particularly Examples I-VI and the general guidance provided in the specification for timing and dosages, set forth at p. 7, line 16 through p. 10, line 10, it would be routine for one of ordinary skill in the art to determine that the invention is operative in a particular species, and to practice the invention in all species in which the invention is operative. Applicants submit that in vivo experiments in rats can reasonably be used to predict the effect of growth factors on the in vivo proliferation of liver cells of animals in general and mammals in particular. (This is addressed in more detail in section (5).) The results disclosed in the application would reasonably indicate to one of ordinary skill in the art that the method is generally applicable in a variety of animals. Applicants therefore respectfully suggest that the rejection on these grounds also be withdrawn.

(3) The present invention is an effective method of treating cirrhosis.

Another rejection in the present office action is that it the method is not effective for treating cirrhosis because it does not address pseudolobule formation and fibrinogenesis. "Thus, it is clear that in addition to inducing liver cell proliferation, inhibition or prevention of pseudolobule formation and fibrinogenesis or resolution of fibrosis in a cirrhotic liver are needed to effectively treat or prevent cirrhosis of the liver." (Jan. 17, 2002 OA, p. 6). The Fujimoto and Ueki references are cited in the office action in support of the rejection. Applicants respectfully traverse this rejection.

Initially, it is important to clearly delineate this issue from the issue discussed relating to gene delivery and expression (discussed in section (4)). The issue relating to gene delivery and expression deals with the question of "how to use" the invention. The issue of therapeutic effect deals more with whether a person of ordinary skill in the art, based on Applicant's disclosure and submitted evidence, would deem the claimed invention "useful" to achieve:

a) "a method of treating diseases associated with the liver" (claims 28-50), and

b) "a method for treating or preventing cirrhosis of the liver" (claim 51).

Cf. In re Brana, 34 USPQ2d 1436 (Fed. Cir. 1995) (delineating the issue of asserted specific use of a compound and the issue of whether one skilled in the art would have reasonably questioned the asserted usefulness based on the disclosure and the submitted evidence.) In other words, assuming that the claimed method can be practiced with gene delivery and expression, (which Applicants have demonstrated is achievable), the question is whether one skilled in the art would reasonably question and continue to question (after reviewing all of the evidence) the therapeutic feasibility of using gene vectors to treat diseases associated with the liver.

Therapeutic "feasibility" is emphasized because as the Federal Circuit has held and in very strong words, expressed to the PTO, clinical efficacy is not the standard for patentability:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant prove regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by the case law years ago. [citing numerous prior cases]

Id. at 1439

> FDA approval ... is not a prerequisite for finding a compound useful within the meaning of patent laws.... Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating the incentive to pursue, through research and development, potential cures in may crucial areas such as the treatment of cancer.

Id. at 1442-43.

"The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Id. This test by the Federal Circuit envisions that there are going to be inventions that have promising pre-clinical data that actually fails in human studies, as many unapproved but patented drugs or therapies have shown. The rationale for this test, as clearly articulated by the Federal Circuit is to prevent elimination of the incentive to pursue, through research and development, potential cures in many crucial areas. Thus, the present application should not be disadvantaged by a lack of human clinical data, because the standard for patentability is less strict than the standard for receiving permission to do clinical trials, which the Applicants would have to first obtain before offering human data.

The office action first cites the Fujimoto article, which uses gene therapy to inject HGF (hepatocyte growth factor) DNA into liver cells. The DNA then is translated by the cellular machinery and HGF is produced which, Fujimoto claims, counteracts cirrhosis. Fujimoto states that "the ideal strategy for the treatment of liver cirrhosis should include prevention of fibrinogenesis, stimulation of hepatocyte mitosis and reorganization of the liver architecture." (Abstract). The office action also cites Ueki for the proposition that HGF gene therapy in rats was effective in

inhibiting accumulation of fibrous connective tissue. The Fujimoto article was published in 2000 and the Ueki article was published in 1999. (Fujimoto was the last author on the Ueki article, so it appears that the 2000 article was an extension of the research offered in the 1999 article.)

Fujimoto and Ueki support a finding of enablement contrary to reasons stated in the office action. Applicants here note, and will discuss further below, that both of these articles that are either contemporary with or postdate the priority date of the present invention, and effectively use gene therapy. Both articles also encourage the use of HGF, and in fact, HGF may be used in conjunction with the present invention.

The present invention teaches a method of treating liver and liver-related diseases by both stimulating the proliferation of liver cells using an unexpectedly effective combination of T3 and KGF, and optionally, the transfection of liver cells to produce any desired gene product in those proliferating cells. The expressed product contained within the vector could be anything, including HGF, meaning that the present invention certainly does not exclude treatment of fibrinogenesis of the liver and should not be construed as such. Any RNA, polypeptide, or protein that ameliorates fibrinogenesis could be inserted into the vector of the present invention and is thus contemplated by it.

Further, the method of treatment claims are just that: a method of treatment, and not necessarily a cure. But the invention does not need to be a cure for liver-related diseases or cirrhosis because those skilled in the art would not interpret the claims in that way. "Although the PTO must give claims their broadest reasonable interpretation, this interpretation must be consistent with the one that those skilled in the art would reach." *In re Cortright*, 165 F.3d 1353 (Fed. Cir. 1999). In *Cortright*, the Federal Circuit reversed the Board's rejection of a method of restoring hair growth

under Section 112, first paragraph. The Federal Circuit held that the Board mistakenly construed "restoring hair growth" to mean "returning the user's hair to its original state," because one of ordinary skill would not so construe the terms in that manner in light of the disclosure. The Federal Circuit found that the "restoring hair growth" language was supported by the disclosure in Cortright, which provided results reflecting "three times as much hair growth as two months earlier." Id. at 1358. The claims of the present application claim a method of treating, not a method of curing. Applicants' disclosure supports the method of treatment claims, as discussed further below.

On page 6, the office action implies that HGF, which according to the references addresses prevention of fibrinogenesis, is key to the treatment of cirrhosis. Because of the apparent emphasis placed on HGF, Applicants find it worthwhile to note that they did contemplate and apply a formulation of HGF in one experiment, but found that it did not have a significant impact on the proliferative characteristics and transduction efficiency on liver cells. Applicants did find that HGF might have offer a small advantage, however. (Spec, p. 10, lines 11-15).

The therapeutic effect of the present invention is the proliferation of healthy hepatocytes and optionally also the expression of any product that treats liver disease produced in the proliferating hepatocytes. It is important to keep in mind that the present invention teaches not only increasing proliferation of liver cells, but also the transfection of any desired gene into the proliferating cells. These proteins, polypeptide, or RNA's that can be generated using the present method could produce any therapeutic effect and the same efficacy that the protein would have if it were introduced into the body by another method or produced endogenously in the cells.

(4) The gene therapy methods of the present invention are not unpredictably vague.

The office action states on page 7 that "at the time of filing, gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable." The Office Action cites Verma et al Nature 389:239-242, 1997 (hereinafter "Verma article"), Marshall, Science, Vol. 269, p. 1054, col. 3, para. 2 and p. 1055, col. 1, 1995 (hereinafter "Marshall"), Orkin et al. "Report and recommendations of the panel to assess the NIH investment in research on gene therapy," p. 1, para. 3 and p. 8, para. 2 ("Orkin"), and Davern et al., Digestive Diseases, v. 16, p. 23 37, 1998 ("Davern"), for the proposition that there have been problems with delivery and expression in gene therapy. Applicants respectfully disagree that, at the time of filing the present application, the methods of gene therapy taught therein were not enabled.

The Liver is an Important Target for Gene Therapy

The liver is the largest gland in the body, making up about 2% of the body weight. It is central to the metabolism of proteins and lipids, hence is an important commercial target for gene therapy (Deonarain, Exp. Opin. Ther. Patents, 1998). Indeed, since the 1980s an increasing number of gene therapy approaches have been targeting the liver because of the recognition of its critical role in intermediary metabolism and its involvement in a large variety of diseases, a great number of which carry extremely poor prognoses (Ledley et al., Proc. Natl. Acad. Sci. Vol 84 pp. 5335-5339, August 1987). There are many advantages to the use of the liver as a target organ for gene therapy. It is highly active metabolically, has a rich blood supply, and a relatively slow turnover of cells (Grove and Wu, Advanced Drug Delivery Reviews 30 (1998), 199-204).

Inborn and acquired errors of liver function, including bleeding disorders involving factor X (Le et al., Blood, Vol 89, No 4 (February 15), 1997: pp 1254-1259) and protein C deficiencies (Cai et al., J Clin Invest 1998 Jun 15; 101(12):2831-41), as well as disorders of lipid metabolism such as hypercholesterolemia caused by LDL receptor deficiencies (Davern and Sharschmidt, Dig Dis 1998; 16:23-37) may be treated by gene therapy. In addition, because of its ability to secrete proteins into the blood stream and GI tract, the liver is an excellent target for the ectopic expression of gene products to correct for their deficiency in diseases of other organs, such as insulin-dependent diabetes caused by the destruction of pancreatic beta-cells (Kolodka et. al. Proc. Natl. Acad. Sci. Vol. 92 pp.3293-3297 April 1995).

Liver failure due to diseases such as cirrhosis, fulminant hepatitis, or cancer currently requires liver transplantation. According to the United Network for Organ Sharing (UNOS), the national patient waitlist for liver transplants included 15,561 registrations as of June 17, 2000, while the liver transplants performed in 1999 numbered 4,698. The National Institutes of Health (NIH) predict that the number of patients needing liver transplants will increase even further in the coming years. Gene therapy in the liver may represent the only therapeutic alternative for those patients with liver failure who are either too low on the waiting list or ineligible for transplantation due to contraindications or failure to meet the minimal criteria for placement on the transplant waiting list (Lucey et al. Liver Transplantation and Surgery, Vol 3, 628-637, 1997). Thus, because of its involvement in numerous inborn as well as acquired metabolic errors and the prevalence, importance, and lack of effective treatment against diseases such as viral hepatitis, cirrhosis, and liver cancer, the liver represents a natural target organ for gene therapy (Ruiz et al., Journal of Viral Hepatitis, 1999, 6, 17-34).

Gene therapy as utilized in the present invention was not unpredictably vague in 1999.

A key issue in an examination of the references is date that the references were published in relation to the date of priority for the present application. The present application claims priority to 1999, which is two years after the Verma reference was published, four years after both the Marshall and Orkin references were published, and a year after the Davern reference was published. Clearly, the state of the art is progressing quickly in gene therapy and what one skilled in the art would have known in 1995 or 1997 is far less than what the one of skill in the art would know in 1999. It is inapposite to cite articles about the level of skill in a quickly advancing art that significantly predate the priority date of an application because the level of skill can rapidly progress, as in the instant situation.

Applicants note that the "level of predictability in the art" is but one factor in the consideration of enablement and that "all evidence related to each of [the] factors" must be considered and "conclusion of nonenablement must be based on the evidence as a whole." MPEP §2164.01(a). The office action recites the Wands factors, so there is no need to repeat them here. The Office Action is not supported by any 1999 or more recent evidence that would raise a reason to doubt the objective truth of the statements contained in the specification, which must be relied on for enabling support. See MPEP §2164.04.

As evidence of the rapid progress, both Fujimoto (1999) and Ueki (2000) effectively use gene therapy techniques. Applicants assert that this reinforces the argument that the state of the art in gene therapy progresses very quickly and that, in 1999, gene therapy was feasible and not wildly unpredictable. The fact that the office action cites these two articles supports this assertion.

The 1997 Verma Article, states, in the bolded introduction, "thanks to better delivery systems, there is hope that the technique will succeed." Even in 1997, Verma acknowledged that better delivery systems, leading to more cells expressing the gene of interest better, faster, and/or more efficiently would be the key to successful gene therapy. The present invention provides such a method. Verma indicates that a common problem with viral vectors is that transcription of the gene is shut off. Even so Verma, in 1997, managed to overcome the problems with gene therapy by using a strong promoter and obtained sustained expression of their gene of choice for two years, the life-span of the animal. (p. 240, 2nd col.). The Verma article concludes that "in the not too distant future, gene therapy will become as routine a practice as heart transplants are today." Obviously, Verma believed that problems with gene therapy were surmountable as of 1997; the present invention provides one such method for making the treatment of liver diseases more routine.

The 1998 Davern article also indicates progress in the field of hepatic gene therapy and, immediately following the quote from the office action that acknowledges the hurdles of gene therapy, states: "Cautious optimism is warranted. With the objectives now clearly in focus and basic immunology, virology and molecular biology rapidly being applied to this burgeoning technology, we anticipate accelerating progress towards the clinical application of gene therapy for liver disease." (p. 35). This statement, made a year before the priority date of the present application, shows that spectators of hepatic gene therapy believed that there was much potential in the field. Applicants suggest that the present invention is an example of that progress.

(5) Rat systems are effective models of human systems.

The office action also states that there is "unpredictability of extending the results of animal systems to humans." (OA, p. 9). The present invention uses male Wistar rats. Applicants traverse this rejection.

The rat is an excellent model for gene therapy because there are many rat models for human diseases (Kolodka et al., Somat Cell Mol Genet 1993 Sep;19(5):491-7). Gene therapy approaches that have used the rat as a model include retroviral vector-mediated expression of human protein C in the rat liver (Cai et al., J. Clin. Invest. Vol 101, No 12, June 1998, 2831-2841), human hepatocyte growth factor in rat skeletal muscle to ameliorate drug-induced lethal liver cirrhosis (Ueki et al., Nature Medicine Vol. 5, No. 2, February 1999), adenovirus-mediated expression of a dominant-negative TGF-beta receptor in the rat liver to attenuate persistent liver fibrosis (Qi et al., Proc. Natl. Acad. Sci. USA, Vol. 96, pp. 22345-2349, March 1999), HSV-tk gene expression in the classical model of liver carcinogenesis in the rat (Gerolami, et al. Cancer Research 60, 993-1001, February 15, 2000), and expression of superoxide dismutase in a rat model of liver transplantation to prevent reperfusion injury.

The common use of the rat as a model for human disease combined with the fact that drug-induced cirrhosis in rats is very similar to the pathology found in the human cirrhotic liver (Fujimoto, J. Gastroenterology and Hepatology (2000) 15 (Suppl.) D33-D36), that many human proteins are functionally active in the rat (Cai, Ueki) and that the rat model for human hepatocellular carcinoma is considered a classical model, far superior to its murine counterpart (Gerolami), are clear evidence that the rat is an excellent model for gene therapy.

Thus, given the present claim amendments and the reasoning presented above, Applicants respectfully request that all 112(1) rejections be withdrawn.

35 U.S.C. §112, ¶2

Applicants have amended the claims to overcome the definiteness rejection as suggested by the office action with the exception of the amendments to claims 26, 28, and 51, wherein the office action suggested eliminating the term "concurrently." Applicants have chosen instead to remove the term "a composition comprising" because the key to the invention is not necessarily that an effective amount of T3 and an effective amount of KGF must be in the same composition (although they certain can be). It is instead that both compounds must be administered concurrently. The term "concurrently" is defined in the specification at p. 10, line 16 though page 11, line 5. Thus, all indefiniteness rejections have been addressed and Applicants respectfully request that these rejections be withdrawn.

CONCLUSION

In view of the foregoing, it is submitted that the claims are allowable, and issuance of a Notice of Allowance is respectfully requested. Applicants hereby request a two-month extension of time. The Commissioner is authorized to charge any fees required by the filing of these papers, and to credit any overpayment to Lyon & Lyon's Deposit Account No. **12-2475**. If Applicants can do anything more to expedite this application, Applicants ask the Examiner to contact the undersigned at (213) 489-1600.

Respectfully submitted,

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Dated: June 17, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES

26. (Amended) A method for improving the efficiency of *in vivo* liver cell retroviral transduction, the method comprising, inducing a semi-synchronous wave of *in vivo* liver cell proliferation by concurrently administering [a composition comprising] tri-iodothyronine (T3) and keratinocyte growth factor (KGF), and further comprising administering to the liver a retroviral vector complexed with cationic liposomes subsequent to the induction of liver cell proliferation, thereby increasing transduction efficiency.

27. The method of claim 26, the cationic liposome comprising DiOctadecylamidoGlycylSpermine (DOGS).

28. (Amended) A method of treat[ment]ing diseases associated with the liver comprising:

inducing a semi-synchronous wave of liver cell proliferation by concurrently contacting the liver cells with [a composition comprising] tri-iodothyronine (T3) and keratinocyte growth factor (KGF);

contacting the liver cells with a retroviral vector containing a nucleic acid that encodes [the]a RNA, protein or polypeptide to be expressed;

and expressing the RNA, protein or polypeptide.

29. (Amended) The method of claim 28, [further comprising inducing]wherein the liver cell proliferation is induced in vitro.

30. (Amended) The method of claim 28, [further comprising inducing]wherein the liver cell proliferation is induced in vivo.

31. (Amended) The method of claim 28, wherein the RNA [comprises]is ribozymal[es] RNA.

32. (Amended) The method of claim 28, wherein said RNA [comprises]is anti-sense RNA.

33. The method of claim 28, wherein the nucleic acid comprises DNA.

34. The method of claim 28, wherein the nucleic acid comprises RNA.

35. (Amended) A method of treat[ment]ing diseases associated with the liver comprising,

the administration of a composition comprising an effective amount of tri-iodothyronine (T3) and an effective amount of keratinocyte growth factor (KGF) , wherein the composition is in an effective amount that induces a semi-synchronous wave of liver cell proliferation upon administration *in vivo* in a subject;

and further comprising administering to the liver, subsequent to the liver cell proliferation, a retroviral vector containing a [the] nucleic acid that encodes [the]a RNA, protein or polypeptide to be expressed, wherein expression of the RNA, protein or polypeptide will treat a condition;

expressing the RNA, protein or polypeptide, thereby treating the condition.

36. The method of claim 35 wherein the effective amount of T3 is ranging from about 400 µg per kg of body weight of the subject to about 40 mg per kg of body weight of the subject.

37. The method of claim 36, wherein the effective amount of T3 is about 4 mg per kg of body weight of the subject.

38. The method of claim 35, wherein the effective amount of KGF is ranging from about 100 µg per kg of body weight of the subject to about 10 mg per kg of body weight of the subject.

39. The method of claim 38, wherein the effective amount of KGF is about 1 mg per kg of body weight of the subject.

40. (Amended) The method of claim 35, wherein the effective amount of T3 and the effective amount of KGF is in a ratio of about 4:1[by weight].

41. The method of claim 40, wherein the effective amount of T3 is in a dose of about 4 mg per kg of body weight of the subject and the effective amount of KGF is in a dose of about 1 mg per kg of body weight of the subject.

42. The method of claim 41, wherein the composition is administered subcutaneously.

43. The method of claim 41, wherein the composition is administered intravenously.

46. The method of claim 41, wherein the composition is administered intramuscularly.

47. The method of claim 41, wherein the composition is administered intraperitoneally.

46. The method of claim 41, wherein the composition is administered directly into the liver.

47. (Amended) The method of claim 35, the retroviral vector [further comprising]complexed with a cationic liposome.

48. The method of claim 47, the cationic liposome comprising DiOctadecylamidoGlycylSpermine (DOGS).

49. (Amended) The method of claim 35 wherein the retroviral vector is administered between about 6 hours and 14 days after administration of the [pharmaceutical]composition.

50. (Amended) The method of claim 35 wherein the retroviral vector is administered between about 24 hours and 8 days after administration of the [pharmaceutical]composition.

51. (Amended) A method for treating or preventing cirrhosis of the liver comprising concurrently administering to a subject [a composition comprising]an effective amount of T3 and an

effective amount of KGF, thereby inducing a semi-synchronous wave of liver cell proliferation *in vivo*, which treats or prevents cirrhosis of the liver.